ON A MATHEMATICAL MODEL OF TUMOR GROWTH BASED ON CANCER STEM CELLS

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Abstract. We consider a simple mathematical model of tumor growth based on cancer stem cells. The model consists of four hyperbolic equations of first order to describe the evolution of different subpopulations of cells: cancer stem cells, progenitor cells, differentiated cells and dead cells. A fifth equation is introduced to model the evolution of the moving boundary. The system includes non-local terms of integral type in the coefficients. Under some restrictions in the parameters we show that there exists a unique homogeneous steady state which is stable.

1. **Introduction.** The development and growth of a tumor is a complicated phenomenon which involves many different aspects from the sub-cellular scale (gene mutation or secretion of substances) to the body scale (*metastasis*).

It is well known that tumors are composed of a heterogeneous mix of cells and other substances, as nutrients and chemicals. Experiments during the last decades confirmed the existence of subpopulation of *Cancer Stem Cells* (CSC) inside the tumors of most cancer's types. CSC exhibit similar characteristics that stem cells, as the capacity of self-renewal and represent only about 1% of the tumor (see for instance [1], [3] or [9] for more details).

In the last years, CSC have focused the interest of an important part of the specialized community in the field. Recent studies have identified populations of CSC in an increasing list of cancer types. Experimental studies evidence CSC as responsible for the long-term survival of some type of cancer after therapies, while other experiments are focused on the role of CSC in metastatic progression of cancer (see [2]), nevertheless the knowledge about these cells is still limited.

Systems of PDE's to model tumor growth have been studied in the last 40 years. During these years, the models have been classified following different criteria: free boundaries, stochastic terms etc. In this work we study a mathematical model which takes into consideration different types of cells: CSC, progenitor cancer cells and differentiated cancer cells modeled as a free boundary problem. The model is considered for the early stage of the cancer when the tumor size is small and necrosis is not present. Experiments show that the growth of the tumor at this stage follows an exponential growth.

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CSC′s mitosis may originate two CSC or two progenitor cells through symmetric division or one of each class through asymmetric division. Regulation of symmetric or asymmetric division is a complex process which depends on a range of conditions, as concentration of cytokines, growth factors etc, existing in the microenvironment of the cell (see for instance [3] and references there). The regulation process still posseses several steps not well understood.

In [7] a system of ordinary differential equations is introduced to model the presence of CSC in the tumor. The authors consider several types of cells: CSC, differentiated cells, cells in an intermediate stage between CSCs and differentiated cells called *progenitor cells* which appear at different stages and finally death cells.

The article is organized as follows. In Section 2 we describe the mathematical model, which consists of a system of hyperbolic equations with a moving boundary. Sections 3 and 4 are devoted to the mathematical analysis of the system with special emphasis to the stability of the unique steady state under a suitable set of restrictions in the parameters and a simplification of the model. We prove that, for a range of parameters there exists a unique homogeneous steady state which is stable. The proof follows a sub- and super-solutions argument where a system of Ordinary Differential Equations is introduced. The conclusions are presented in the last section.

2. **Modelling.** In order to describe the mathematical model we introduce the following notation and the hypothesis listed below.

- "s" cancer stem cells density,
- "p" progenitor cells density,
- "m" differentiated cells density,
- "d" death cells density,
- "v" velocity of tumor cells within the tumor,
- "$\Omega(t)$" the interior of the tumor,
- "$\partial\Omega(t)$" the boundary of the tumor.

H1 The different type of cells are physically identical with a continuous distribution into the tumor.

H2 Cells interact through the exchange of molecules and may evolve spontaneously from one state to another, depending on their initial state and the microenviroment.

H3 The CSC division process is regulated by a chemical feedback with the cell′s neighborhood which determines the type of division (symmetric or asymmetric). We consider that the rate of growth of CSC is a nonlocal function k_s^s which depends explicitly or implicitly on the concentration of CSC in the neighborhood of the cell. We consider a general non-local expression for the growth rate function

$$k_s^s(x,t) = k_0 - \frac{1}{|\Omega(t)|}\int_{\Omega(t)} k_1(t,x,y)s(y,t)dy \tag{1}$$

where k_1 is a positive function which measures the influence of the concentration of CSC in the tumor. Particular expressions of k_1 are proposed below

Case I.

$$k_s^s(x,t) = k_0 - \int_{|x-y|\leq\epsilon} k_1(|x-y|)s(y,t)dy$$

where k_1 is a positive function depending on the distance between the cells.
Case II.
k_1 is the green function of a particular partial differential operator of parabolic or elliptic type. For instance $k_s^s = k_0 - z$ where z is the solution to the the parabolic problem

$$\kappa z_t - \Delta z + \lambda z = s$$

or the elliptic problem

$$-\Delta z + \lambda z = s$$

with the appropriate boundary conditions.

H4 CSC may produce progenitor cells at ratio k_s^p in a similar way that in the previous hypothesis. We assume

$$k_s^p := k_2 + \int_{\Omega(t)} k_3(x, y) s(y, t) dy. \tag{2}$$

H5 p-cells can either self-renew or they can differentiate into m-cells at constant rates k_p^p and k_p^m respectively.

H6 We assume that m-cells have a neglected capacity to proliferate, and therefore the corresponding rate growth factor does not appear.

H7 We assume that subpopulation tumor cells p and d die at constant rates k_p and k_d respectively and decompose at rate k_d. The death rate of SCS is assumed null.

Assumption H1 and H2 are frequently used in continuous models of differential equations where different types of cells are mixed (see for instance [4] or [8]). Constant rates for proliferation and death of cells (i.e. assumptions H5, H6 and H7) are also used in [7], [8] and [6] for instance. Coefficients depending on the concentration of nutrients are described in [4] for the first stage of the tumor and it is natural to assume that death of cells is produced by apoptosis (assumption H7). Assumptions H3 and H4 are introduced in this work in order to obtain the rate of growth of CSC. Nonlocal terms of integral type have been used in mathematical modeling by a long list of authors. In [10] the authors suggest a growth coefficient rate for the cancer cells which considers the influence of the immediate surrounding of a cell to replicate itself. The coefficient in [10] is given in the form

$$\mu_1 \left(1 - \int_\Omega k_{1,1}(x, y) u(y) dy - \int_\Omega k_{1,2}(x, y) v(y) dy \right),$$

where "u" and "v" denote cancer cells density and *extracellular matrix* density respectively. The nonlocal term describes the "competition" for the space between cancer cells and extracellular matrix.

Following [4] we consider a continuous motion of cells within the tumor due to the proliferation and death of cancer cells. The tumor tissue is treated as a porous medium and the moving cells as fluid flow. The velocity v of the fluid flow is described by Darcy′s law

$$v = -\beta \nabla \sigma$$

where σ is the pressure of the fluid and β is a positive constant assumed 1. Then, the evolution of subpopulation of cancer cells are described by the following system of first order hyperbolic equations.

$$
\begin{aligned}
&\frac{\partial s}{\partial t} + div(vs) = k_s^s s - k_s^p s, && 0 < t < T, \quad x \in \Omega(t),\\
&\frac{\partial p}{\partial t} + div(vp) = k_s^p s + k_p^p p - k_p^m p - k_p p, && 0 < t < T, \quad x \in \Omega(t),\\
&\frac{\partial m}{\partial t} + div(vm) = k_p^m p - k_m m, && 0 < t < T, \quad x \in \Omega(t),\\
&\frac{\partial d}{\partial t} + div(vd) = k_p p + k_m m - k_d d, && 0 < t < T, \quad x \in \Omega(t),
\end{aligned}
\tag{3}
$$

where the coefficients k_s^s, k_s^p, k_p^m, k_p, k_m and k_d are described in H1-H7. For simplicity we assume that coefficients k_1 and k_3 introduced to define k_s^s and k_s^p in (1) and (2) are constant and therefore k_s^s and k_s^p are defined by

$$
k_s^s = k_0 - \frac{k_1}{|\Omega(t)|}\int_{\Omega(t)} s \quad \text{and} \quad k_s^p = k_2 + \frac{k_3}{|\Omega(t)|}\int_{\Omega(t)} s. \tag{4}
$$

The system (3) is completed with appropriate initial data

$$
s(0,x) = s_0(x), \quad p(0,x) = p_0(x), \quad m(0,x) = m_0(x) \quad \text{and} \quad d(0,x) = d_0(x)
$$

in $|x| \in \Omega_0$. In [7], the growth rates k_s^s and k_s^p are assumed constant, the reader can find there explicit values of the rest of the parameters. CSC represents. The conservation of the mass laws for the densities of the cells, assumed homogeneous tumor density, gives

$$
s + p + m + d = constant = N, \tag{5}
$$

where the constant N is assumed 1. From (5) we can obtain an explicit expression for the density of m-cells as a function of s, p and d, i.e. $m = 1 - s - p - d$ and the system (3) can be simplified to

$$
\begin{aligned}
&\frac{\partial s}{\partial t} + div(vs) = k_s^s s - k_s^p s, && 0 < t < T, \quad x \in \Omega(t),\\
&\frac{\partial p}{\partial t} + div(vp) = k_s^p s + k_p^p p - k_p^m p - k_p p, && 0 < t < T, \quad x \in \Omega(t),\\
&\frac{\partial d}{\partial t} + div(vd) = k_p p + k_m(1 - s - p - d) - k_d d, && 0 < t < T, \quad x \in \Omega(t),
\end{aligned}
$$

assumed

$$
s_0 + p_0 + m_0 + d_0 = 1.
$$

We add equations in (3) and thanks to (5) we have the balance of the mass given by

$$
div(v) = k_s^s s + k_p^p p - k_d d \quad \text{for} \quad 0 < t < T, \quad x \in \Omega(t). \tag{6}
$$

For simplicity we assume radially symmetric distribution of cells and spherical tumors, i.e. $\Omega(t) := \{x \in \mathbb{R}^3, \ \text{such that } |\mathrm{x}| \leq \mathrm{R(t)}\}$ where $R(t)$ denotes the radius of the tumor. By continuity we assume that the velocity of the free boundary is equal to the velocity of the fluid flow at the boundary (see for instance [4])

$$
\frac{dR}{dt} = v(R(t),t) \qquad \text{for} \qquad t > 0. \tag{7}
$$

We assume throughout the paper that the initial data s_0, p_0, m_0 and d_0 are regular functions, in the sense of continuous and bounded functions, satisfying

$$
0 < s_0 < 1, \qquad 0 < p_0 < 1, \qquad 0 < m_0 < 1 \quad \text{and} \quad 0 < d_0 < 1 \qquad \text{in} \quad \overline{\Omega}_0. \tag{8}
$$

In section 4 we consider the following extra assumptions.

H8 At the early stage the volume of the components derived from death cells decomposition (mainly water) described by the term $k_d d$ may be neglected as compared by the growth capacity of the proliferating cells "p" (modelized by the term "$k_p^p p$") i.e.

$$k_d d << k_p^p p. \tag{9}$$

Notice that assumption (9) is only introduced for the early stage of the tumor. For posterior stages (as necrotic tumors) (9) can not be assumed.

H9 Experiments show that the mitosis cycle of CSC is smaller that mitosis cycle of proliferating cells. Consequently we assume

$$k_s^p s << k_p^p p. \tag{10}$$

Assumptions (9) and (10) are used in Section 4 to simply the system and study the stability of the steady state.

As a consequence of a large number of parameters we reduce our work to the following case:

$$s^* := \frac{k_0 - k_2 - k_p^p + k_p^m k_p}{k_1 + k_3} \in (0, 1) \tag{11}$$

$$k_s^{s*} := k_0 - k_1 s^* > 0, \qquad k_s^{p*} := k_2 + k_3 s^* > 0 \tag{12}$$

$$p^* := \frac{k_s^{s*}(1 - s^*) - k_s^{p*}}{k_p^p} \in (0, 1) \tag{13}$$

$$k_1(1 + s*) - k_0 = -\mu < 0, \tag{14}$$

and

$$s^* + p^* \leq 1. \tag{15}$$

Notice that as a consequence of (14) we have

$$k_0 - k_1 > 0. \tag{16}$$

In Section 4 we see that (s^*, p^*) is an steady state of a simplified system. To have a biological meaningful steady state we impose assumptions (11), (13) and (15). Assumption (16) is introduced by technical reasons in order to prove that the steady state is stable. (16) gives a growth rate of stem cells k_s^s large enough, in the sense that

$$k_s^{s*} = k_0 - k_1 s^* > k_1.$$

3. **Mathematical analysis.** We introduce the spacial variable $r \in I := (0, 1)$ such that

$$r := \frac{|x|}{R(t)}.$$

Since

$$\nabla \cdot (vs) = s\nabla \cdot v + v \cdot \nabla s = s(k_s^s s + k_p^p p - k_d d) + \frac{v}{R}\frac{\partial s}{\partial r}$$

the system (3), (6), (7) and (8) becomes

$$\frac{\partial s}{\partial t}+\left(-r\frac{\dot R}{R}+\frac{v}{R}\right)\frac{\partial s}{\partial r} = k_s^s s-k_s^p s+s(-k_s^s s-k_p^p p+k_d d), \tag{17}$$

$$\frac{\partial p}{\partial t}+\left(-r\frac{\dot R}{R}+\frac{v}{R}\right)\frac{\partial p}{\partial r} = k_s^p s+p(k_p^p-k_p^m-k_p-k_s^s s-k_p^p p+k_d d), \tag{18}$$

$$\frac{\partial m}{\partial t}+\left(-r\frac{\dot R}{R}+\frac{v}{R}\right)\frac{\partial m}{\partial r} = k_p^m p-k_m m+m(-k_s^s s-k_p^p p+k_d d), \tag{19}$$

$$\frac{\partial d}{\partial t}+\left(-r\frac{\dot R}{R}+\frac{v}{R}\right)\frac{\partial d}{\partial r} = k_p p+k_m m-k_d d+d(-k_s^s s-k_p^p p+k_d d), \tag{20}$$

$$\frac{\partial}{\partial r}(r^2\frac{v}{R}) = r^2(k_s^s s+k_p^p p-k_d d), \tag{21}$$

with boundary conditions

$$v(1,t)=\frac{dR}{dt} \quad \text{and} \quad v(0,t)=0 \tag{22}$$

and initial data

$$s(r,0)=s_0, \quad p(r,0)=p_0, \quad m(r,0)=m_0, \quad d(r,0)=d_0 \quad \text{and} \quad R(0)=R_0. \tag{23}$$

Notice that by integration in (21) and thanks to (22)

$$\frac{v(1,t)}{R(t)}=\int_I r^2(k_s^s s+k_p^p p-k_d d)$$

and

$$\frac{dR}{dt}=v(1,t)=R(t)\int_I r^2(k_s^s s+k_p^p p-k_d d). \tag{24}$$

Let ϕ be defined by

$$\phi(x):=\begin{cases} 0 & \text{if} \quad x\le 0,\\ x & \text{if} \quad 0<x\le 1,\\ 1 & \quad\quad \text{otherwise.}\end{cases}$$

In the following lemma we proof that the solution satisfies

$$0\le s\le 1, \qquad 0\le p\le 1, \qquad 0\le m\le 1 \quad \text{and} \quad 0\le d\le 1 \tag{25}$$

provided (8). For technical reasons we introduce $\phi(s)$ to replace s in the integral part of the coefficients k_s^s and k_s^p for the proof of Lemma 3.1. Once we prove that the solutions satisfy (25) we may eliminate the auxiliary function ϕ.

Lemma 3.1. *Under assumption (8) we have that the solution satisfies (25).*

Proof. Let H_ϵ be the regularized Heaviside function and denote by $(\,\cdot\,)_+$ the positive part function. Notice that

$$\lim_{\epsilon\to 0} sH_\epsilon(s)=(s)_+.$$

We also consider the functions ψ_ϵ, ψ, Ψ_ϵ and $\Psi : I\!R\to I\!R$ defined by

$$\psi_\epsilon(x):=\begin{cases} -1, & x\le-\epsilon,\\ \frac{1}{\epsilon}x, & -\epsilon<x<0,\\ 0, & x\ge 0,\end{cases} \qquad \psi(x):=\begin{cases} -1, & x<0,\\ 0, & x\ge 0,\end{cases}$$

$$\Psi_\epsilon(x) := \begin{cases} -x - \frac{\epsilon}{2}, & x \le -\epsilon, \\ \frac{1}{2\epsilon}x^2, & -\epsilon < s < 0, \\ 0, & x, \ge 0, \end{cases} \qquad \Psi(x) := \begin{cases} -x, & x, \le 0, \\ 0, & x, \ge 0. \end{cases}$$

Notice that $\Psi'_\epsilon = \psi_\epsilon$ and

$$\lim_{\epsilon \to 0} \psi_\epsilon = \psi; \qquad \lim_{\epsilon \to 0} \Psi_\epsilon = \Psi \quad \text{ and } \quad x\psi(x) = \Psi(x) \;\; \text{for} \;\; x \in I\!R.$$

We multiply equation (17) by $-r^2\psi_\epsilon(s)$ and integrate over I to take limits as $\epsilon \to 0$ to obtain

$$\begin{gathered} \frac{d}{dt}\int_I r^2\Psi(s) + \int_I r^2\left(-r\frac{\dot{R}}{R} + \frac{v}{R}\right)\frac{\partial \Psi(s)}{\partial r} = \\ \int_I r^2\psi(s)(k_s^s s - k_s^p s - s^2 k_s^s - k_p^p ps + k_d ds). \end{gathered} \tag{26}$$

We notice that the second term in the left hand side part of (26) can be expressed in a simpler way:

$$\frac{1}{2}\int_I r^2\left(-r\frac{\dot{R}}{R} + \frac{v}{R}\right)\frac{\partial \Psi(s)}{\partial r} = \frac{3\dot{R}}{R}\int_I r^2\Psi(s) - \frac{1}{R}\int_I r^2\Psi(s)\frac{1}{r^2}\frac{\partial r^2 v}{\partial r} \tag{27}$$

by (21) we have that

$$\frac{1}{R}\int_I \Psi(s)\frac{\partial r^2 v}{\partial r} = \int_I r^2\Psi(s)(k_s^s s + k_p^p p - k_d d). \tag{28}$$

Thanks to (27), (28) and the equality $\Psi(s) = s\psi(s)$, (26) becomes

$$\frac{d}{dt}\int_I r^2\Psi(s) + \frac{3\dot{R}}{R}\int_I r^2\Psi(s) = \int_I r^2\psi(s)(k_s^s s - k_s^p s) = \int_I r^2\Psi(s)(k_s^s - k_s^p).$$

Since $k_s^s - k_s^p \le k_0 - k_2$, it results

$$\frac{d}{dt}\int_I r^2\Psi(s) \le \left(k_0 - k_2 - \frac{3\dot{R}}{R}\right)\int_I r^2\Psi(s).$$

By Gronwall's lemma we deduce that $s \ge 1$. In the same way, and using that s is a positive function we prove that $p \ge 0$ which implies that $m \ge 0$ and $d \ge 0$. Since $s + p + m + d = 1$ the proof ends. □

Remark 1. Previous lemma and (24) implies that there exists a constant c_0 which depends on k_0, k_1, k_2, k_3 and k_d such that

$$\left|\dot{R}\right| R^{-1} \le c_0 < \infty$$

and after integration we deduce $R(t) \in [R_0 e^{-c_0 t}, R_0 e^{c_0 t}]$.

Theorem 3.2. *Under assumptions (8), the system (17)-(23) has a unique global solution.*

The proof follows a straightforward argument based on Banach fixed point theorem in the appropriate functional spaces for local existence. Thanks to Lemma 3.1 and Remark 1 we have global existence. Uniqueness is a consequence of the Banach fixed point argument. Similar computations can be found in [5] where more details are given. The solution is also Lipchitz continuous.

4. **Stability of the steady states for a simplified model.** Under assumptions (9) and (10), equations (17), (18) and (21) become

$$\frac{\partial s}{\partial t} + \left(-r\frac{\dot{R}}{R} + \frac{v}{R}\right)\frac{\partial s}{\partial r} = k_s^s s - k_s^p s + s(-k_s^s s - k_p^p p), \tag{29}$$

$$\frac{\partial p}{\partial t} + \left(-r\frac{\dot{R}}{R} + \frac{v}{R}\right)\frac{\partial p}{\partial r} = k_p^p p - k_p^m p - k_p p + p(-k_s^s s - k_p^p p), \tag{30}$$

$$\frac{\partial}{\partial r}(r^2\frac{v}{R}) = r^2(k_s^s s + k_p^p p), \tag{31}$$

with boundary conditions

$$v(1,t) = \frac{dR}{dt} \quad \text{and} \quad v(0,t) = 0, \tag{32}$$

and initial data

$$s(r,0) = s_0, \quad p(r,0) = p_0 \quad \text{and} \quad R(0) = R_0. \tag{33}$$

As in Lemma 3.1, we introduce the function ϕ in the coefficients k_s^s and k_s^p such that

$$k_s^s = k_0 - 3k_1\int_I r^2\phi(s) \quad \text{and} \quad k_s^p = k_2 + 3k_3\int_I r^2\phi(s). \tag{34}$$

Once we prove $s \le 1$ we may eliminate ϕ.

Lemma 4.1. *The solution to the system (29)-(33), for k_s^s and k_s^p defined in (34) satisfies*

$$0 \le s \le 1 \quad \textit{and} \quad 0 \le p \le 1.$$

Proof. As in Lemma 3.1 we multiply (29) by $\psi_\epsilon(s)$ and (30) by $\psi_\epsilon(p)$ and integration over I. We take limits as $\epsilon \to 0$ and thanks to Gronwall′s lemma we conclude

$$s \ge 0 \quad \text{and} \quad p \ge 0.$$

In order to obtain the upper bound we add both equations

$$\begin{gathered}\frac{\partial}{\partial t}(s+p) + \left(-r\frac{\dot{R}}{R} + \frac{v}{R}\right)\frac{\partial}{\partial r}(s+p) = \\ (s+p-1)(-k_s^s s - k_p^p p) - p(k_p^m + k_p) - k_s^p s.\end{gathered} \tag{35}$$

By (34) and (16) we know that

$$0 < k_0 - k_1 \le k_s^s \le k_0, \qquad k_2 \le k_s^p \le k_2 + k_3. \tag{36}$$

Multiply (35) by $r^2 H_\epsilon(s+p-1)$ and proceed as in Lemma 3.1 to obtain

$$\frac{d}{dt}\int_I r^2(s+p-1)_+ =$$

$$-3\frac{\dot{R}}{R}\int_I r^2(s+p-1)_+ - \int_I r^2 H(s+p-1)(p(k_p^m + k_p) + k_s^s s).$$

Remark 1 and (36) implies that

$$\frac{d}{dt}\int_I r^2(s+p-1)_+ \le 3R_0 e^{c_0 t}\int_I r^2(s+p-1)_+.$$

Gronwall′s lemma and (8) end the proof. ∎

Remark 2. As a consequence of the previous lemma and (16), we have

$$k_s^s > k_0 - k_1 > 0, \quad \text{and} \quad k_2 < k_s^p < k_2 + k_3. \tag{37}$$

In order to study the asymptotic behaviour of the solutions we introduce the following system of ODE's

$$\overline{s}' = \overline{s}(k_s^s - k_s^p - k_s^s\overline{s} - k_p^p\underline{p}), \tag{38}$$

$$\underline{s}' = \underline{s}(k_s^s - k_s^p - k_s^s\underline{s} - k_p^p\overline{p}), \tag{39}$$

$$\overline{p}' = \overline{p}((k_p^p - k_p^m - k_p) - k_s^s\underline{s} - k_p^p\overline{p}), \tag{40}$$

$$\underline{p}' = \underline{p}((k_p^p - k_p^m - k_p) - k_s^s\overline{s} - k_p^p\underline{p}), \tag{41}$$

with initial data $\overline{s}_0$, $\underline{s}_0$, $\overline{p}_0$ and $\underline{p}_0$ satisfying

$$0 < \underline{s}_0 < s^* < \overline{s}_0 \leq 1, \qquad 0 < \underline{p}_0 < p^* < \overline{p}_0 \leq 1 \tag{42}$$

and k_s^s and k_s^p defined in (4) by

$$k_s^s = k_0 - 3k_1 \int_I r^2 s \quad \text{and} \quad k_s^p = k_2 + 3k_3 \int_{\Omega(t)} r^2 s. \tag{43}$$

Notice that the system can be expressed as two independent systems of ODEs.

$$\begin{cases} \overline{s}' = \overline{s}(k_s^s - k_s^p - k_s^s\overline{s} - k_p^p\underline{p}), \\ \underline{p}' = \underline{p}(k_p^p - k_p^m - k_p - k_s^s\overline{s} - k_p^p\underline{p}) \end{cases}$$

$$\begin{cases} \underline{s}' = \underline{s}(k_s^s - k_s^p - k_s^s\underline{s} - k_p^p\overline{p}), \\ \overline{p}' = \overline{p}((k_p^p - k_p^m - k_p) - k_s^s\underline{s} - k_p^p\overline{p}). \end{cases}$$

Lemma 4.2. *Under assumption (42), there exists a unique global solution to (38)-(41) satisfying*

$$0 < \underline{s} < \overline{s} \leq 1 \quad \textit{and} \quad 0 < \underline{p} < \overline{p} \leq 1. \tag{44}$$

Proof. Notice that the right hand side terms in the system are polynomial in the unknowns with continuous and positive coefficients. Then, we have existence and uniqueness of solutions in $C^1(0, T_{max})$ for some $T_{max} \leq \infty$ such that

$$|T_{max}| + |\overline{s}| + |\underline{s}| + |\overline{p}| + |\underline{p}| = \infty.$$

Since $\overline{s} \equiv 0$ is a solution to (38), by uniqueness of solutions we have that $\overline{s} > 0$ for positive initial data. In the same way we obtain that $\underline{s} > 0$, $\overline{p} > 0$ and $\underline{p} > 0$.

In order to end the proof we argue by contradiction. Let us assume that there exists $t_0 < T_{max}$ such that

$$\underline{s} < \overline{s} \quad \text{and} \quad \underline{p} < \overline{p}, \qquad \text{for } t < t_0$$

and

$$(\underline{s} - \overline{s})(\underline{p} - \overline{p}) = 0, \qquad \text{at } t = t_0.$$

- If $\underline{s}(t_0) = \overline{s}(t_0)$, then $\underline{s}'(t_0) \geq \overline{s}'(t_0)$ and therefore $\underline{p}(t_0) \geq \overline{p}(t_0)$.
- If $\underline{p}(t_0) = \overline{p}(t_0)$, then $\underline{p}'(t_0) \geq \overline{p}'(t_0)$ which implies $\underline{s}(t_0) \geq \overline{s}(t_0)$.

So, necessarily

$$\underline{s}(t_0) = \overline{s}(t_0), \qquad \underline{p}(t_0) = \overline{p}(t_0),$$

and the backward solution satisfies

$$\underline{s}(0) = \overline{s}(0), \qquad \underline{p}(0) = \overline{p}(0)$$

which contradicts assumption (43). As a consequence of Lemma 4.1 and (16), the following inequalities hold

$$k_s^p > 0, \qquad k_p^p \underline{p} > 0$$

and then

$$\overline{s}' \leq k_s^s \overline{s}(1 - \overline{s})$$

for a positive coefficient k_s^s. By assumption (42) we have that $\overline{s} \leq 1$ for $t \leq T_{max}$. In the same way we proof that $\overline{p} \leq 1$ for $t \leq T_{max}$. To end the proof we notice that, since the solutions and the coefficients are uniformly bounded, we get that $T_{max} = \infty$. □

Theorem 4.3. *We assume*

$$0 < \underline{s}_0 \leq s_0 \leq \overline{s}_0 \text{ and } \quad 0 < \underline{p}_0 \leq p_0 \leq \overline{p}_0, \tag{45}$$

then

$$\underline{s} \leq s \leq \overline{s} \quad \text{ and } \quad \underline{p} < p < \overline{p}$$

for any $t > 0$.

Proof. We consider the following functions defined by

$$\overline{S} = s - \overline{s}, \qquad \underline{S} = s - \underline{s}, \qquad \overline{P} = p - \overline{p} \quad \text{and} \quad \underline{P} = p - \underline{p}.$$

Notice that $\overline{S}$ satisfies the equation

$$\begin{aligned} \tfrac{\partial \overline{S}}{\partial t} + \left(-r\tfrac{\dot{R}}{R} + \tfrac{v}{R}\right) \tfrac{\partial \overline{S}}{\partial r} &= s(k_s^s - k_s^p - k_s^s s - k_p^p p) - \overline{s}(k_s^s - k_s^p - k_s^s \overline{s} - k_p^p \underline{p}) \\ &= \overline{S}[k_s^s - k_s^p - k_s^s s - k_p^p p] + \overline{s}(-k_s^s(s - \overline{s}) - k_p^p(p - \underline{p})). \end{aligned} \tag{46}$$

We multiply (46) by $r^2 H_\epsilon(\overline{S})$ and integrate over I. We take limits as $\epsilon \to 0$ to get

$$\begin{aligned} &\frac{\partial}{\partial t} \int_I r^2 (\overline{S})_+ + \int_I r^2 \left(-r\frac{\dot{R}}{R} + \frac{v}{R}\right) \frac{\partial (\overline{S})_+}{\partial r} = \\ &\int_I r^2 (\overline{S})_+ [k_s^s - k_s^p - k_s^s s - k_p^p p] + \int_I r^2 H(\overline{S}) \overline{s}(-k_s^s(s - \overline{s}) - k_p^p(p - \underline{p})). \end{aligned} \tag{47}$$

The second term in the left hand side part of (47) is treated in the following way

$$\int_I r^2 \left(-r\frac{\dot{R}}{R} + \frac{v}{R}\right) \frac{\partial (\overline{S})_+}{\partial r} = 3\frac{\dot{R}}{R} \int_I r^2 (\overline{S})_+ - \int_I (\overline{S})_+ \frac{1}{R} \frac{\partial r^2 v}{\partial r}.$$

Thanks to (31) the last term in the previous equation is simplified to

$$-\int_I r^2 (\overline{S})_+ \frac{1}{r^2 R} \frac{\partial r^2 v}{\partial r} = -\int_I r^2 (\overline{S})_+ (k_s^s s + k_p^p p). \tag{48}$$

We consider the last term in the right hand side part of (47)

$$\int_I r^2 H(\overline{S}) \overline{s}(-k_s^s(s - \overline{s}) - k_p^p(p - \underline{p})) \leq \overline{s} \int_I r^2 (-k_s^s (\overline{S})_+ + k_p^p \Psi(\underline{P})). \tag{49}$$

Therefore thanks to (47)–(49) we have

$$\frac{\partial}{\partial t}\int_I r^2(\overline{S})_+ \leq \left(-3\frac{\dot{R}}{R} - k_s^s\overline{s}\right)\int_I r^2(\overline{S})_+ + \overline{s}k_p^p\int_I r^2\Psi(\underline{P}).$$

In the same way we obtain the following inequalities for $\underline{S}$, $\overline{P}$ and $\underline{P}$

$$\frac{\partial}{\partial t}\int_I r^2\Psi(\underline{S}) \leq \left(-3\frac{\dot{R}}{R} + k_s^s - k_s^p + k_s^s\underline{s}\right)\int_I r^2\Psi(\underline{S}) - \underline{s}k_p^p\int_I r^2\overline{P}_+,$$

$$\frac{\partial}{\partial t}\int_I r^2(\overline{P})_+ \leq \left(-3\frac{\dot{R}}{R} + (k_p^p - k_p^m - k_p(1+\overline{p}))\overline{p}\right)\int_I r^2(\overline{P})_+ + \ \overline{p}k_s^s\int_I r^2\Psi(\underline{S})$$

and

$$\frac{\partial}{\partial t}\int_I r^2\Psi(\underline{P}) \leq \left(-3\frac{\dot{R}}{R} + (k_p^p - k_p^m - k_p(1+\underline{p})\underline{p}\right)\int_I r^2\Psi(\underline{P}) - \underline{p}k_s^s\int_I r^2\overline{S}_+.$$

Summing up the above expressions and thanks to Remark 1 and (37) we obtain

$$\frac{\partial}{\partial t}\int_I r^2[(\overline{S})_+ + \Psi(\underline{S}) + (\overline{P})_+ + \Psi(\underline{P})] \leq k(t)\int_I r^2[(\overline{S})_+ + \Psi(\underline{S}) + (\overline{P})_+ + \Psi(\underline{P})]. \quad (50)$$

Since the initial data s_0 and p_0 satisfy (45) we have that

$$\int_I r^2\left((\overline{S})_+ + \Psi(\underline{S}) + (\overline{P})_+ + \Psi(\underline{P})\right)\Big|_{t=0} = 0.$$

We apply Gronwall′s lemma to end the proof. ☐

Lemma 4.4. *Under assumptions (11)-(14) there exist a unique steady state of the system (38)-(42) $\underline{s}^*$, $\overline{s}^*$, $\underline{p}^*$ and $\overline{p}^*$ satisfyng*

$$s^* = \underline{s}^* = \overline{s}^* = 3\int_I r^2 s \quad \text{and} \quad p^* = \underline{p}^* = \overline{p}^*,$$

for s^* and p^* defined in (11) and (13) respectively.

Proof. We consider the case where s does not depend on t, i.e. k_s^s and k_s^p are given constants. Then

$$k_s^s - k_s^p = k_s^s s + k_p^p p \quad (51)$$

we replace in (39) to obtain

$$\begin{aligned} k_p^p - k_p^m - k_p &= k_s^s - k_s^p \\ &= k_0 - k_2 - (k_1 + k_3)3\int_I r^2 s. \end{aligned}$$

Therefore

$$3\int_I r^2 s = \frac{k_0 - k_2 - k_p^p + k_p^m + k_p}{k_1 + k_3} > 0.$$

Then s^*, p^* defined en (11) and (13) satisfies (38)-(41). The uniqueness is a consequence of the linearity in p of (51). ☐

Lemma 4.5. *Under assumption (42), the solution $\underline{s}$, $\overline{s}$, $\underline{p}$ and $\overline{p}$ to (38)-(41) satisfy*

$$\underline{s} \leq s^* \leq \overline{s} \quad \text{and} \quad \underline{p} < p^* < \overline{p},$$

for s^* and p^* defined in (11) and (13) respectively.

Proof. We consider k_s^{s*} and k_s^{p*} defiend in (12) and the following functions

$$\overline{S}^* = \overline{s} - s^*, \qquad \underline{S}^* = \underline{s} - s^*, \qquad \overline{P}^* = \overline{p} - p^* \quad \text{and} \quad \underline{P}^* = \underline{p} - p^*.$$

Thanks to Lemma 4.4 we know that

$$k_s^{s*} - k_s^{p*} - k_s^s s^* - k_p^p p^* = 0$$

then $\overline{S}^*$ satisfies

$$\frac{d}{dt}\overline{S}^* = \overline{s}((k_s^s - k_s^{s*}) - (k_s^p - k_s^{p*}) - (k_s^s\overline{s} - k_s^{s*}s^*) - k_p^p(\underline{p} - p^*)).$$

Notice that

$$\begin{aligned} -(k_s^s\overline{s} - k_s^{s*}s^*) &= -(k_s^s - k_s^{s*})\overline{s} - k_s^{s*}\overline{S}^* \\ &= k_1 3\int_I r^2(s - s^*)\overline{s} - k_s^{s*}\overline{S}^* \end{aligned}$$

and

$$(k_s^s - k_s^{s*}) - (k_s^p - k_s^{p*}) = (k_1 + k_3)\left(s^* - 3\int_I r^2 s\right).$$

Then we have

$$\frac{d}{dt}\overline{S}^* = \overline{s}\left((k_1(1-\overline{s}) + k_3)\left(s^* - 3\int_I r^2 s\right) - k_s^{s*}\overline{S}^* - k_p^p\underline{P}^*\right).$$

Thanks to (44) we have that $(k_1(1-\overline{s}) + k_3) > 0$ and Theorem 4.3 implies

$$s^* - 3\int_I r^2 s \geq 0 \quad \text{if} \quad \overline{s} = s^*.$$

Therefore, it results

$$\frac{d}{dt}\overline{S}^* \geq -\overline{s}k_p^p\underline{P}^* \quad \text{if} \quad \overline{S}^* = 0.$$

In the same way, if $\overline{S}^* \geq 0$

$$\begin{aligned} -(k_s^s\overline{s} - k_s^{s*}s^*) &= -(k_s^s - k_s^{s*})\overline{s} - k_s^{s*}\overline{S}^* \\ &= k_1(3\int_I r^2 s - s^*)\overline{s} - k_s^{s*}\overline{S}^* \\ &\leq k_1(\overline{s} - s^*) - k_s^{s*}\overline{S}^* \\ &= (k_1(1+s^*) - k_0)\,\overline{S}^* \\ &= -\mu\overline{S}^* \end{aligned}$$

we have

$$\frac{d}{dt}\underline{P}^* \leq -\overline{p}\left(\mu\overline{S}^* + k_p^p\underline{P}^*\right) \quad \text{if} \quad \overline{S}^* \geq 0.$$

We consider the approximated problem

$$\begin{cases} \overline{s}_\epsilon' = \overline{s}_\epsilon(k_s^s - k_s^p - k_s^s\overline{s}_\epsilon - k_p^p\underline{p}_\epsilon), \\ \underline{p}_\epsilon' = \underline{p}_\epsilon(k_p^p - k_p^m - k_p - k_s^s\overline{s}_\epsilon - k_p^p\underline{p}_\epsilon) - \epsilon, \end{cases}$$

with the initial data

$$\overline{s}_\epsilon(0) = \overline{s}_0 \qquad \underline{p}_\epsilon(0) = \underline{p}_0.$$

Notice that

$$\overline{s} < \overline{s}_\epsilon \leq 1, \qquad \underline{p}_\epsilon < \underline{p}.$$

We introduce the following functions

$$\overline{S}^*_\epsilon = \overline{s}_\epsilon - s^* \quad \text{and} \qquad \underline{P}^*_\epsilon = \underline{p}_\epsilon - p^*$$

which satisfy

$$\begin{aligned}
\tfrac{d}{dt}\overline{S}^*_\epsilon &= \overline{s}_\epsilon \left((k_1(1-\overline{s}_\epsilon) + k_3)\left(s^* - 3\int_I r^2 s\right) - k_s^{s*}\overline{S}^*_\epsilon - k_p^p \underline{P}^*_\epsilon \right), \\
\tfrac{d}{dt}\underline{P}^*_\epsilon &= \underline{p}_\epsilon \left(-k_1 s^* \left(s^* - 3\int_I r^2 s\right) - k_s^s \overline{S}^*_\epsilon - k_p^p \underline{P}^*_\epsilon \right) - \epsilon.
\end{aligned}$$

As before we have that

$$\frac{d}{dt}\overline{S}^*_\epsilon \geq -\overline{s}_\epsilon k_p^p \underline{P}^*_\epsilon, \quad \text{if} \quad \overline{S}^*_\epsilon = 0$$

and

$$\frac{d}{dt}\underline{P}^*_\epsilon < -\overline{p}_\epsilon \left(\mu \overline{S}^*_\epsilon + k_p^p \underline{P}^*_\epsilon \right) \quad \text{if} \quad \overline{S}^*_\epsilon \geq 0.$$

We argue by contradiction and assume that there exists $t_0 < \infty$ such that

$$\overline{S}^*_\epsilon \underline{P}^*_\epsilon = 0 \quad \text{for} \quad t = t_0 \quad \text{and} \quad \overline{S}^*_\epsilon \underline{P}^*_\epsilon < 0 \quad \text{for} \quad t < t_0.$$

If $\overline{S}^*_\epsilon = 0$ at t_0, by the regularity of the solutions we have that $\frac{d}{dt}\overline{S}^*_\epsilon \leq 0$ and therefore

$$\underline{P}^*_\epsilon = 0, \qquad \frac{d}{dt}\underline{P}^*_\epsilon < 0 \quad \text{at } t = t_0$$

which is a contradiction and proves

$$\overline{S}^*_\epsilon > 0 \quad \text{for } t = t_0.$$

If $\underline{P}^*_\epsilon = 0$ for $t = t_0$ we have that

$$\frac{d}{dt}\underline{P}^*_\epsilon < 0 \quad \text{at } t = t_0$$

which contradicts the regularity of $\underline{P}^*_\epsilon$ and proves

$$\overline{S}^*_\epsilon > 0, \qquad \underline{P}^*_\epsilon < 0 \quad \text{for any } t > 0.$$

Taking limits when $\epsilon \to$ we obtain

$$\overline{S}^* \geq 0, \qquad \underline{P}^* \leq 0 \quad \text{for } t > 0.$$

In the same fashion we prove

$$\underline{S}^* \leq 0, \qquad \overline{P}^* \geq 0 \quad \text{for } t > 0$$

and the proof ends. □

Lemma 4.6. *Under assumption (43), the solution $\underline{s}$, $\overline{s}$, $\underline{p}$ and $\overline{p}$ to (38)-(41) satisfy*

$$|\overline{s} - \underline{s}| + |\overline{p} - \underline{p}| \leq c(|\overline{s}_0 - \underline{s}_0| + |\overline{p}_0 - \underline{p}_0|) \quad \textit{for} \quad t > 0$$

and

$$c := 2s^* \left(\frac{(\overline{s}_0 - \underline{p}_0)(\overline{p}_0 - \underline{p}_0)}{(\overline{s}_0 - \underline{s}_0 + \overline{p}_0 - \underline{p}_0)\underline{s}_0\, \underline{p}_0} + \underline{p}_0 \right) \leq \frac{2s^*}{\underline{s}_0\, \underline{p}_0}. \tag{52}$$

Proof. We divide (38) by $\overline{s}$ and (39) by $\underline{s}$ to obtain

$$\frac{\overline{s}'}{\overline{s}} = (k_s^s - k_s^p - k_s^s\overline{s} - k_p^p\underline{p}),$$
$$\frac{\underline{s}'}{\underline{s}} = (k_s^s - k_s^p - k_s^s\underline{s} - k_p^p\overline{p}).$$

Thanks to the above expressions we get

$$\frac{d}{dt}\ln\frac{\overline{s}}{\underline{s}} = -k_s^s(\overline{s}-\underline{s}) + k_p^p(\underline{p}-\overline{p}).$$

In the same way we have

$$\frac{d}{dt}\ln\frac{\overline{p}}{\underline{p}} = k_s^s(\overline{s}-\underline{s}) - k_p^p(\underline{p}-\overline{p})$$

and then

$$\frac{d}{dt}\left(\ln\frac{\overline{s}}{\underline{s}} + \ln\frac{\overline{p}}{\underline{p}}\right) = 0.$$

After integration it results

$$\left(\ln\frac{\overline{s}}{\underline{s}} + \ln\frac{\overline{p}}{\underline{p}}\right) = k > 0$$

for $k = \ln\frac{\overline{s}_0\,\overline{p}_0}{\underline{s}_0\,\underline{p}_0}$. Then

$$\frac{\overline{s}}{\underline{s}} \le e^k \quad \text{and} \quad \frac{\overline{p}}{\underline{p}} \le e^k \tag{53}$$

i.e.

$$e^{-k}\overline{s} \le \underline{s} \quad \text{and} \quad e^{-k}\overline{p} \le \underline{p}$$

and thanks to Lemma 4.5 we have

$$e^{-k}s^* \le \underline{s} \quad \text{and} \quad e^{-k}p^* \le \underline{p}.$$

From (53) we have

$$\overline{s} - \underline{s} \le (e^k - 1)\underline{s} \quad \text{and} \quad \overline{p} - \underline{p} \le (e^k - 1)\underline{p}$$

and as a consequence of (42)

$$|\overline{s} - \underline{s}| + |\overline{p} - \underline{p}| \le 2s^*\left(\frac{\overline{s}_0\,\overline{p}_0}{\underline{s}_0\,\underline{p}_0} - 1\right).$$

Notice that

$$\frac{\overline{s}_0\,\overline{p}_0}{\underline{s}_0\,\underline{p}_0} - 1 = \frac{1}{\underline{s}_0\,\underline{p}_0}(\overline{p}_0|\overline{s}_0 - \underline{s}_0| + \underline{s}_0|\overline{p}_0 - \underline{p}_0|)$$

and also

$$\frac{\overline{s}_0\,\overline{p}_0}{\underline{s}_0\,\underline{p}_0} - 1 = \frac{1}{\underline{s}_0\,\underline{p}_0}(\underline{p}_0|\overline{s}_0 - \underline{s}_0| + \overline{s}_0|\overline{p}_0 - \underline{p}_0|).$$

Then, by linear optimization we have

$$2s^*\left(\frac{\overline{s}_0\,\overline{p}_0}{\underline{s}_0\,\underline{p}_0} - 1\right) \le c(|\overline{s}_0 - \underline{s}_0| + |\overline{p}_0 - \underline{p}_0|).$$

where

$$c := 2s^*\left(\frac{(\overline{s}_0 - \underline{p}_0)(\overline{p}_0 - \underline{p}_0)}{(\overline{s}_0 - \underline{s}_0 + \overline{p}_0 - \underline{p}_0)\underline{s}_0\,\underline{p}_0} + \underline{p}_0\right).$$

$\square$

Theorem 4.7. *The homogeneous steady state defined by*

$$s = s^* \quad \text{and} \quad p = p^*$$

is stable in the sense that

$$\|s - s^*\|_{L^\infty} + \|p - p^*\|_{L^\infty} \le 2c(\|s_0 - s^*\|_{L^\infty} + \|p_0 - p^*\|_{L^\infty})$$

for c defined in (52).

Proof. Notice that, by Theorem 4.3

$$\|s - s^*\|_{L^\infty} + \|p - p^*\|_{L^\infty} \le |\overline{s} - s^*| + |\underline{s} - s^*| + |\overline{p} - p^*| + |\underline{p} - p^*|,$$

where $\overline{s}$, $\underline{s}$, $\overline{p}$ and $\underline{p}$ are the solutions to (38)-(42) for initial data

$$\overline{s}_0 = \max\{\sup\{s_0\}, s^*\}, \qquad \underline{s}_0 = \min\{\inf\{s_0\}, s^*\},$$
$$\overline{p}_0 = \max\{\sup\{p_0\}, p^*\}, \qquad \underline{p}_0 = \min\{\inf\{p_0\}, p^*\}.$$

Thanks to Lemma 4.5 and Lemma 4.6 we have that

$$|\overline{s} - s^*| + |\underline{s} - s^*| + |\overline{p} - p^*| + |\underline{p} - p^*| \le |\overline{s} - \underline{s}| + |\overline{p} - \underline{p}| \le c(|\overline{s}_0 - \underline{s}_0| + |\overline{p}_0 - \underline{p}_0|)$$

for c defined in (52). Since

$$|\overline{s}_0 - \underline{s}_0| \le 2\|s_0 - s^*\|_{L^\infty} \quad \text{and} \quad |\overline{p}_0 - \underline{p}_0| \le 2\|p_0 - p^*\|_{L^\infty}$$

we get

$$\|s - s^*\|_{L^\infty} + \|p - p^*\|_{L^\infty} \le 2c(\|s_0 - s^*\|_{L^\infty} + \|p_0 - p^*\|_{L^\infty})$$

and the proof ends. □

5. **Conclusions and discussion.**

In this paper we propose a simple mathematical model to describe the solid tumor growth based on Cancer Stem Cells (CSC). The model describes the evolution of spherical tumor at the early stage where necrosis is not present. The modeling follows [7] where a system of Ordinary Differential Equations is considered. We include transport terms in the system following the mass balance principle and nonlocal terms of integral type to model the birth rate of stem cells. The system is simplified to obtain that, under some restrictions in the parameters, there exists a unique steady state which is stable.

We assume that growth factor of proliferating cells $k_p^p p$ is larger than the degradation factor of death cells, and the term $k_d d$ is neglected. This assumption is valid for the early stage and the degradation term should be included to model later stage. After chemotherapy the distribution of subpopulation of cells changes as a consequence of the difference of the times of mitosis. Recent studies show that the percentage of stem cells in the tumor stabilizes at a constant steady state. The simplified mathematical model describes the stability of the steady state, nevertheless the asymptotic stability of both models remains open. The inclusion of the term $k_d d$ may produce a change in the stability of the system.

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